REMARKS

The above amendment to claim 1 introduces no new matter. Applicants respectfully note that the above amendment was made to facilitate prosecution and not in acquiescence to the Examiner's rejection. Applicants reserve the right to pursue subject matter deleted with this amendment at a later date.

Claims 1 and 3-5 are pending and stand rejected. Applicants gratefully acknowledge that the Examiner has found convincing certain of Applicant's arguments in their response filed April 25, 2003, and that rejections of record not reiterated in the present Office Action have been overcome.

Double Patenting

The Office Action states that claims 1, 3 and 4 continue to stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 5,856,642 for the reasons of record. The Office Action further acknowledges Applicant's commitment to filing a Terminal Disclaimer to this patent should any of the currently pending claims be found allowable, and Applicants respectfully continue to request that this rejection be held in abeyance until such allowable subject matter is found.

Rejection under 35 U.S.C. §102(a)

The Office Action continues to reject claim 1 under 35 U.S.C. § 102(a) as being anticipated by Krieg (WO/962555 or Krieg et al. (1996) Antisense & Nucleic Acid Drug Development 6: 133-9). In particular, the Office Action states that, despite Applicant's arguments that the inverted CpG taught by Krieg *et al.* is fortuitous, "the structure of the instant claim 1 and that of the prior art appear identical."

Applicants respectfully note for the record that the structural distinction between the claimed "inverted CpG" antisense compositions and the "natural" GpC linkages taught by Krieg *et al.* exists inasmuch as an "inverted CpG" GpC antisense sequence will be non-complementary to its target mRNA sequence, while a naturally-occurring GpC antisense sequence will be fully

complementary to its target mRNA sequence. Nevertheless, in order to advance prosecution of the instant application, and not in acquiescence to this rejection, Applicants have amended claim 1 to delete the relevant "inverted CpG" compositions from the claimed CpG modification Markush group. Applicants respectfully reserve the right to pursue this deleted subject matter at a later date. As the pending rejection under 35 U.S.C. §102(b) is obviated by this amendment, Applicants respectfully request withdrawal of the rejection.

Rejection under 35 U.S.C. §112, first paragraph (enablement)

The Office Action continues to reject method claims 3 and 4, and new claim 5, under 35 U.S.C. §112 because "the specification, while being enabling for methods of using the contemplated compounds in cell culture, does not reasonably provide enablement for methods of treating mammals or methods of therapy using the instantly contemplated compounds." In response to Applicants arguments of record, the Office Action states that while "Applicants' claims are directed to antisense-mediated gene inhibition....none of the *in vivo* data provided shows antisense-mediated gene inhibition."

In support of enablement of the claimed invention, Applicants hereby submit (1) evidence that the exemplary oligonucleotides taught by the specification cause a beneficial antisense-mediated inhibition of target gene expression *in vivo*; and (2) further evidence and argument that the teachings of the specification are commensurate with the scope of the claimed invention.

First, Applicants hereby provide evidence, in the form of publications, showing the efficacy of the modified CpG antisense oligonucleotides of the present invention for repressing gene expression *in vivo*, while reducing the immunomodulatory effects on the treated organism. In particular, the Agrawal and Zhao reference (Exhibit A; (1998) Antisense and Nucleic Acid Drug Development 8: 135-9), demonstrates that substitution of 2'-O-methylribonucleosides for CpG deoxynuclosides minimizes immune stimulation (compare results obtained with unmodified oligo 2 to those obtained with 2'-O-methyl modified oligo 3 of the same sequence in Figure 1). Notably, this publication evidences the retention of antisense-mediated antitumor effects of the modified CpG oligo (see last line of final paragraph on page 138). In particular, the antisense

oligonucleotides used in this study were directed against the RIα subunit of protein kinase A (PKA), and have been shown to both down-regulate RIα subunit expression and inhibit the growth of a human colon cancer tumor in nude mice (see Nesterova and Cho-Chung (1995) Nature Med. 1: 528-33; included here as Exhibit B). Furthermore, RI α-targeted antisense therapy has been shown to effect these changes by selectively down-regulating genes involved in proliferation-transformation while up-regulating genes differentiation-reverse transformation (Exhibit C; Cho *et al.* (2001) Proc. Natl. Acad. Sci. 98: 9819-23).

Second, in order to fully address the scope of arguments made in the enablement rejection, Applicants hereby provide further evidence and argument that the teachings of the specification are commensurate with the scope of the claimed invention. In particular, the Office Action states, in support of the enablement rejection against an antisense-related methods, that "there has been only one antisense drug ever approved by the FDA". In response, Applicants respectfully note that, while the FDA's function is to ensure the health and safety of the food and drugs available in the United States, they do not set the standard for patentability. Indeed, the MPEP explicitly states that "the applicant need not demonstrate that the invention is completely safe" (at MPEP 2164.01(c)), and that the P.T.O. should "not impose on applicants the unnecessary burden of providing evidence from human clinical trials...(because)....there is no decisional law that requires an applicant to provide data from human clinical trials to establish utility for an invention related to treatment of human disorders (see In re Isaacs, 347 F.2d 889, 146 USPQ 193 (CCPA 1963); and In re Langer, 503 F.2d 1380, 183 USPQ 288 (CCPA 1974)), even with respect to situations where no art-recognized animal models existed for the human disease encompassed by the claims. Ex parte Balzarini, 21 USPQ2d 1892 (Bd. Pat. App. & Inter. 1991) (see MPEP 2107.03 (IV)). Accordingly, the cited deficit of FDA-approved antisense therapeutics is not dispositive to the enablement of the claimed invention in this case.

The Office Action has also rejected Applicant's prior argument that the Milner *et al.* reference makes it routine in the art to identify efficacious antisense oligonucleotide sequences. Milner *et al.* provides a high-throughput screening process that allows for the rapid screening of the numerous possible antisense oligo sequences using an *in vitro* microarray system. The Office Action states that, "Applicants' claims are directed to antisense-mediated gene

inhibition....*in vivo*...(and)....results *in vitro* (such as those taught by Milner *et al.*) are not considered predictive of those obtained *in vivo*" (emphasis added).

In response, Applicants respectfully note that the Milner *et al.* reference was cited as exemplary of the many methods available for rapid and efficacious screening of possible oligonucleotide sequences for a given target, and not as the only method required for validating efficaciousness of antisense *in vivo*. In particular, the Milner *et al.* reference provides a simple empirical method of selecting antisense sequences which are effective in heteroduplex formation with a given mRNA target. Indeed, this method is suited to addressing the problem of "access to the target site," which, the Office Action cites as among "several other outstanding issues that the specification fails to resolve." Accordingly, Milner *et al.* resolves one of the issues which the Office Action states is a problem in this field, and, accordingly supports enablement (albeit not in and of itself).

Furthermore, contrary to the assertions of the Office Action that results *in vitro* are not considered predictive of those obtained *in vivo*, the Milner *et al.* reference, along with two other references, have been cited for the principle that "scanning-array technology have shown a good correlation between the hybridization of an ASO (antisense oligonucleotide) to a synthetic RNA and the ability of that ASO to direct RNase H cleavage of the pre-mRNA, both in vitro and in vivo" (emphasis added) (quoting from Disckson *et al.* (2002) Neuromuscular Disorders 12: S67-S70, at S68, top of 2nd column; included here as Exhibit D). Indeed, another of the references cited shows that antisense oligonucleotides directed against cyclin mRNA, which were selected by hybridization to scanning arrays *in vitro*, are effective *in vivo* in Xenopus oocytes (see Sohail *et al.* (2001) Nucleic Acids Research 29: 2041-51; Exhibit E). Still further, numerous other publications in which multiple candidate antisense oligonucleotides are screened for their effectiveness in an *in vivo* (animal) model using only routine skill in the art further demonstrate the enablement of the claimed invention. (see, *e.g.*, Szyf (2002) Methods 27: 184-191 (Exhibit F); and Gleave *et al.* (2001) Urology 58 (supp2A): 39-48 (Exhibit G)).

The Office Action further states repeatedly that Applicants' claims are "drawn very broadly to methods of treating cells *in vivo* or to treating or preventing any condition or disease

suspected of being associated with aberrant gene expression in mammals," but this characterization of Applicants' claimed invention fails to specifically characterize Applicants' contribution to the art, and thereby logically, but unduly, leads to an overdrawn burden upon the Applicants to show enablement. In particular, Applicants are not claiming every method utilizing antisense to treat disease, but rather methods using particular types of modified CpG-containing phosphorothioate oligonucleotides that have reduced undesirable side effects. The particular CpG modifications for use in the method of the invention include: alkylphosphonate-modified CpGs, 2'-O-substituted CpGs, stereospecific phosphorothioate CpGs, phosphotriester CpGs, phosphoramidate CpGs, and 2'-5' CpG's. The scope of enablement must be commensurate with the scope of the claimed invention. To require that Applicants demonstrate efficacious treatment of all diseases associated with aberrant gene expression is undue because Applicants are specifically claiming only the improved methods that utilize the modified CpG oligonucleotides taught.

Further to this point, it is well recognized in the antisense field that undesirable side effects have been a problem in developing effective therapies. Applicants contribution to the art is in the area of diminishing such undesirable side effects by making these particular modifications, not in the area of providing specific new antisense oligonucleotide sequence strings, many of which are already known in the art and have been shown to be useful in diminishing the expression of the targeted gene. Applicants invention may be applied to any of these known antisense oligonucleotide sequence strings using the teachings of the specification and the level of ordinary skill in the art.

Indeed, it is undisputed in the record that many patents have been granted to compositions and methods for treating various diseases using antisense oligonucleotides directed against specific sequences (see *e.g.* U.S. Patent Nos. 6,489,307; 6,479,465; and 6,436,909). It is therefore clear that there are many oligonucleotides which, notwithstanding FDA approval (which was addressed above), have been recognized to meet the standards of patentability for being useful in modulating gene expression (*e.g.*, for the treatment of various diseases and disorders). Whether there are particular inoperative embodiments that can be envisioned, in the form of oligonucleotide sequences which are complementary to a specific mRNA target but not

effective in reducing expression of that mRNA target *in vivo*, is not dispositive to enablement in this case.

Indeed, the Federal Circuit, in its enablement decisions, has emphasized that a patent's claims need not specifically exclude possible inoperative substances in order to be enabled, but rather requires only that the inoperative embodiments be avoidable by the skilled artisan [see Syntex (U.S.A.) Inc. v. Paragon Optical Inc., 7 USPQ2d 1001, which states: "a patent's disclosure complies with 35 U.S.C. § 112 if it defines the desired functional relationship, even if some experimentation is required to reproduce the invention....patent claims that include some claimed combinations which are inoperative are not necessarily invalid under 35 U.S.C. § 112" (citing Atlas Powder Co. v. E. I. duPont de Nemours & Co., 750 F.2d 1569, 1577 (Fed. Cir. 1984); In re Dinh-Nguyen, 492 F.2d 856, 858-59 (C.C.P.A. 1974); and In re Anderson, 471 F 2d 1237, 1242 (C.C.P.A. 1973)); "it is impractical and unreasonable to require a patentee to set out an extended list of precise combinations and formulae since one skilled in the art would avoid obvious inoperative combinations" (citing Ex parte Cole, 223 U.S.P.Q. 94, (C.C.P.A. 1983); and Lever Bros. Co. v. Procter & Gamble Mfg. Co., 139 F.2d 633, 638 (4th Cir. 1943)); and "[I]t is not a function of the claims to specifically exclude . . . possible inoperative substances" (citing Atlas Powder Co., 750 F.2d at 1576)].

Therefore, in view of the many antisense methods that have been shown to be operable *in vivo* in the literature and/or deemed to be operable *in vivo* by the U.S.P.T.O. by the granting of a patent, Applicants respectfully request reconsideration and withdrawal of this rejection.

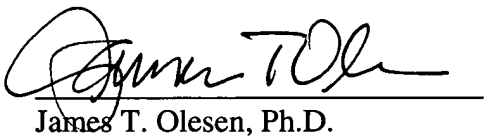
CONCLUSION

Applicant believes that the presently maintained rejections of the pending claims have been fully overcome by the amendment and arguments presented above. Accordingly, Applicant respectfully submits that the pending claims are in condition for allowance, and prompt acknowledgment of such is respectfully requested. If the Examiner believes that any further

discussion of this communication would be helpful, he is encouraged to contact the undersigned by telephone.

No additional fees are believed to be due in connection with this communication, however, please apply any additional charges, or credit any overpayment, to our Deposit Account No. 08-0219.

Respectfully submitted,



James T. Olesen, Ph.D.
Attorney for Applicant
Reg. No.: 46, 967

December 18, 2003
HALE AND DORR LLP
60 State Street
Boston, MA 02109
Tel: (617) 526-6000
Fax: (617) 526-5000